Effects of Hypercapnia on Hemodynamic, Inotropic, Lusitropic, and Electrophysiologic Indices in Humans*

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Study objective: **The inotropic, lusitropic, and electrophysiologic effects of acute hypercapnia in humans are not known. Although the effects of hypercapnia on the systemic circulation have been well documented, there is still some debate as to whether hypercapnia causes true pulmonary vasoconstriction *in vivo*. We have therefore evaluated the effects of acute hypercapnia on these cardiac indices and the interaction of hypercapnia with the systemic and pulmonary vascular beds in humans.**
Participants and interventions: **Eight healthy male volunteers were studied using Doppler echocardiography. After resting for at least 30 min to achieve baseline hemodynamic parameters (T_0), they were rendered hypercapnic to acheive an end-tidal carbon dioxide (CO_2) of 7 kPa for 30 min by breathing a variable mixture of CO_2/air (T_1). They were restudied after 30 min recovery breathing air (T_2). Hemodynamic, diastolic, and systolic flow parameters, QT dispersion (maximum-minimum QT interval measured in a 12-lead ECG), and venous blood samples for plasma renin activity (PRA), angiotensin II (ANG II), and aldosterone (ALDO) were measured at each time point.**
Results: **Hypercapnia compared with placebo significantly increased mean pulmonary artery pressure 14±1 vs 9±1 mm Hg and pulmonary vascular resistance 171±17 vs 129±17 dyne·s·cm^{-5}, respectively. Heart rate, stroke volume, cardiac output, and mean arterial BP were increased by hypercapnia. Indexes of systolic function, namely peak aortic velocity and aortic mean and peak acceleration, were unaffected by hypercapnia. Similarly, hypercapnia had no effect on lusitropic indexes reflected by its lack of effect on isovolumic relaxation time, mitral E-wave deceleration time, and mitral E/A wave ratio. Hypercapnia was found to significantly increase both QTc interval and QT dispersion: 428±8 vs 411±3 ms and 48±2 vs 33±4 ms, respectively. There was no significant effect of hypercapnia on PRA, ANG II, or ALDO.**
Conclusion: **Thus, acute hypercapnia appears to have no adverse inotropic or lusitropic effects on cardiac function, although repolarization abnormalities, reflected by an increase in QT dispersion, and its effects on pulmonary vasoconstriction may have important sequelae in man.**
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Key words: electrophysiologic; hypercapnia; inotropic; lusitropic; pulmonary circulation

Abbreviations: Acc_{mean}=aortic mean acceleration; Acc_{peak}=aortic peak acceleration; ALDO=aldosterone; ANG II=angiotensin II; Av_{max}=maximal velocity of atrial transmitral flow; Av_{peak}=aortic peak velocity; CO=cardiac output; CO_2=carbon dioxide; DBP=diastolic arterial BP; EDT=early transmitral flow deceleration time; EDTc=early transmitral flow deceleration time adjusted for heart rate; $ETco_2$=end-tidal carbon dioxide; Ev_{max}=maximal velocity of early transmitral flow; HR=heart rate; IVRT=isovolumic relaxation time; IVRTc=isovolumic relaxation time adjusted for heart rate; MAP=mean arterial BP; MPAP=mean pulmonary artery pressure; PAT=pulmonary acceleration time; PRA=plasma renin activity; PVR=pulmonary vascular resistance; RAS=renin angiotensin system; RIA=radioimmunoassay; SBP=systolic arterial BP; SV=stroke volume; SVI=aortic systolic velocity integral; SVR=systemic vascular resistance

Hypercapnia is a well-recognized consequence of a variety of disease states. It is frequently encountered in the context of chronic obstructive airways disease and more unusually in disorders of the nervous and musculoskeletal systems. In recent years, there has been much interest in the effects of hypercapnia in anesthetic practice after the finding that mechanical ventilation may contribute to increased morbidity and mortality as a consequence of barotrauma.[1-3] This has resulted in a volume- and pressure-limited ventilation strategy and elevated levels of carbon dioxide (CO_2), so-called permissive hypercapnia.[4,5]

The effects of hypercapnia on the systemic circulation have been well documented,[6,7] although there is still some debate as to whether CO_2 causes true pulmonary vasoconstriction *in vivo*.[8-13] Many of these studies were performed more than 20 years ago and findings were sometimes based purely on changes in mean pulmonary artery pressure (MPAP) and where

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pulmonary vascular resistance (PVR) was measured, it was derived from cardiac outputs (COs) calculated using the Fick principle, with errors a consequence of a changing state of respiratory gas exchange.[14,15]

The advent of newer noninvasive methods such as Doppler echocardiography has permitted a more detailed examination not only of hemodynamic effects but also of inotropic[16,17] and lusitropic[18,19] activity. A novel marker of abnormal myocardial repolarization, QT dispersion,[20,21] has also provided us with information regarding the electrophysiologic effects of different stimuli.

We have therefore evaluated for the first time (to our knowledge) the effects of acute hypercapnia on inotropic, lusitropic, and repolarization indexes and reexamined the interaction between hypercapnia and the pulmonary circulation in the integrated physiologic system of man.

Materials and Methods

Subjects

Eight healthy male volunteers, mean age 24 years (range, 21 to 34 years), were studied. There was no abnormality present on clinical history, examination, 12-lead ECG, echocardiography, biochemical screening, or hematologic screening. Informed written consent to the study protocol, previously approved by the Tayside Committee for Medical Research Ethics, was obtained.

Study Protocol

Subjects attended the clinical laboratory and were studied in a supine position, rolled slightly on the left side. An IV cannula was inserted into the left forearm for blood sampling. Subjects then rested supine for at least 30 min to obtain stable resting hemodynamics (T_0). They were then rendered hypercapnic by breathing a variable mixture of CO_2 and medical air to attain an end-tidal CO_2 (ET_{CO_2}) of 7 kPa for 30 min (T_1) and then they breathed room air for a further 30 min (T_2). The hypercapnic gas mixture was produced from separate cylinders of CO_2 and medical air fitted with variable flow valves. Gases were mixed in a 25-L Douglas bag (Collins Inc; Braintree, Mass) from which the subjects breathed through a mouthpiece connected by a series of one-way valves, while wearing an occlusive nose clip. Measurements of pulmonary and systemic hemodynamic variables, inotropic, lusitropic, and electrophysiologic indexes, and venous blood samples for plasma renin activity (PRA), angiotensin II (ANG II), and aldosterone (ALDO) were taken at T_0, T_1, and T_2.

Measurements

Oxygenation: Arterial blood oxygen saturation was continuously monitored by transcutaneous oximetry (CSI 503; Criticare Systems Inc; Waukesha, Wis). Recordings were averaged at steady state over a period of 5 min at each time point for the purpose of analysis.

End-tidal CO_2: This was measured continuously with the tip of the gas sampling tube adjacent to the mouth of the subject, using a transportable ET_{CO_2} monitor (POET TE; Criticare Systems Inc; Waukesha, Wis). Recordings at steady state were averaged over a period of 5 min and this value was used for the purpose of analysis.

Hemodynamics: Systolic arterial BP (SBP), mean arterial BP (MAP) and diastolic arterial BP (DBP) were measured using a semiautomatic sphygmomanometer (Vital Signs Monitor; Critikon; Tampa, Fla). The mean of three consistent readings was taken at each time point. Heart rate (HR) was recorded on an ECG trace and an average rate over 6 R-R intervals was calculated. Pulmonary acceleration time (PAT) in milliseconds was measured as previously described[22,23] from pulmonary arterial flow by pulsed-wave Doppler echocardiography (Vingmed SD50; Vingmed Sound; Horten, Norway) from the left third/fourth intercostal space. The mean of three consistent waveforms at each time point was used for the purpose of analysis. MPAP in mm Hg was calculated as MPAP=73-(0.42×PAT).[24] Aortic cross-sectional area was measured by M-mode echocardiography (Vingmed SD50). The aortic systolic velocity integral (SVI) was measured by on-line computer-assisted determination using pulsed-wave Doppler echocardiography of ascending aortic blood flow from the suprasternal notch. On-line calculations of stroke volume (SV=SVI×cross-sectional area) and CO as the product of SV and HR were also made. Total PVR was calculated as: $PVR=MPAP/CO\times 80$ dyne·s·cm^{-5}. We have previously shown the short term coefficients for measurement of PAT and SVI to be 1.7% and 1.2%, respectively.[22]

Systolic Flow Parameters: Doppler ascending aortic blood flow (Vingmed SD50) was recorded with a 2.0-MHz pulsed-wave transducer with depth adjusted to give maximal velocity and the following variables were measured: aortic peak acceleration (Acc_{peak}), aortic mean acceleration (Acc_{mean}), and aortic peak velocity (Av_{peak}). We have previously shown the coefficient of variability for the measurement of Acc_{mean} and Av_{peak} by this method to be 12.5% and 4.4%, respectively.[22]

Diastolic Filling Parameters: From the apical window, pulsed-wave Doppler analysis of mitral and diastolic flow was combined with simultaneous phonocardiogram recording with the microphone (Siemens AG; Munich, Germany). Measurements were all made on-line during expiration and in triplicate, with a display sweep speed of 100 mm/s. Transmitral flow was analyzed after adjusting sample volume depth to yield maximal E-wave velocities with clearly defined flow velocity envelopes. Measurement of diastolic flow parameters from these signals has previously been shown to be highly reproducible and easily applicable in our own laboratory[19] and also by other workers.[25] The aortic component of the second heart sound was identified on the phonocardiogram trace by noting closure artifacts from superimposition of aortic Doppler flow profiles. From diastolic transmitral flow, maximal velocities of the early (Ev_{max}) and atrial (Av_{max}) components of flow were measured, and the ratio of Ev_{max} and Av_{max} (E/A ratio) was calculated. In addition, the E-wave deceleration time (EDT) was calculated as the time in milliseconds from peak velocity to the end of the E wave. The isovolumic relaxation time (IVRT) was calculated for the left ventricle as the time in milliseconds from the aortic component of the phonocardiogram second heart sound to the onset of diastolic transmitral flow. Both EDT and IVRT were corrected for changes in HR induced by hypoxemia by dividing by the square root of the simultaneous ECG R-R interval; $EDTc=IVRT/\sqrt{RR}$, $IVRTc=IVRT/\sqrt{RR}$.

QT Interval Measurement: The ECGs from both study days were analyzed in random order after completion of the study, by an investigator who was blinded with respect to the stimulus the volunteers had received. QT interval if feasible was measured in all leads of a surface 12-lead ECG (paper speed=25 mm/s). Three consecutive cycles were measured in each lead where possible and the mean value was taken as representing the QT interval in that lead. QT interval was calculated according to standard criteria[20] from the onset of the QRS complex to the end of the T wave *ie,* a return to the T/P baseline. In the presence of U waves, the QT interval was measured to the nadir of the curve between the T and the U waves.

QT dispersion was defined as the difference between the max-

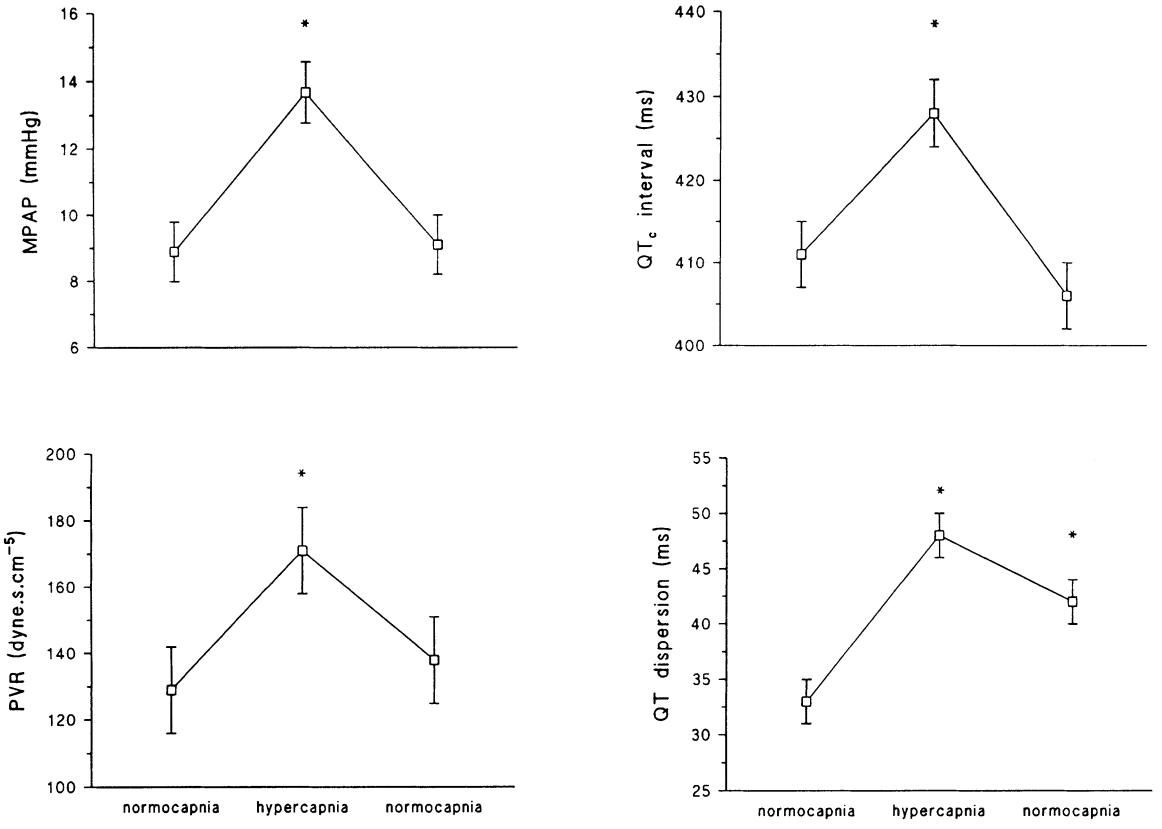

FIGURE 1. Effects of hypercapnia on pulmonary hemodynamics and electrophysiologic parameters. *Top left:* absolute MPAP measured during normoxemia (baseline), after 30 min hypercapnia, and 30 min after rebreathing air, respectively. *Bottom left:* absolute PVR measured during normoxemia (baseline), after 30 min hypercapnia, and 30 min after rebreathing air, respectively. *Top right:* absolute QTc interval measured during normoxemia (baseline), after 30 min hypercapnia, and 30 min after rebreathing air, respectively. *Bottom right:* absolute QT dispersion measured during normoxemia (baseline), after 30 min hypercapnia, and 30 min after rebreathing air, respectively. Asterisk=a significant ($p<0.05$) difference between baseline and hypercapnia or between baseline and after 30 min rebreathing air.

imum and minimum QT interval measured during analysis of all leads of the surface ECG.[20] The measurements were made using a computer-linked digitizing tablet.[26] To compare the standard measure of QT interval with QT dispersion, we calculated the average of six QT intervals in lead II. QT intervals were then corrected for rate using the formula of Bazett[27] ($QTc=QT/\sqrt{RR}$).

RAS Activity: Venous blood samples for plasma ALDO were collected into lithium heparin tubes, and for measurement of plasma renin activity (PRA) into edetic acid tubes, before being centifuged; plasma was stored at -20°C until assayed. PRA was assayed using commercially available radioimmunoassay (RIA) kits (Sorin Biomedica; Saluggia, Italy) that assayed PRA by measurement of amount of angiotensin I generated per hour. ALDO was measured using a similar RIA assay kit (Sorin Biomedica). Samples for ANG II assay were collected into chilled glass tubes containing 0.5 mL of a cocktail comprising 0.05 mmol/L 0-phenanthrolene, 0.2 g neomycin, 0.125 mmol/L edetic acid, and 2% (vol/vol) alcohol before centrifugation, and separated plasma was stored at -70°C. ANG II assay was performed following separation from plasma proteins by alcohol extraction using a specific commercially available RIA kit (Nichols Institute Diagnostics; San Juan Capistrano, Calif). We have previously shown the coefficients of variation for analysis were as follows: ANG II 11.2%; PRA, 7.6%; and ALDO, 8.3%.[28]

Data Analysis

Comparisons between serial time points on the same study day were made using multifactorial analysis of variance followed by Duncan's multiple range test. A probability value of $p<0.05$ (two-tailed) was considered to be statistically significant. Data are presented in the text, tables, and figures as means and SEM.

RESULTS

Oxygenation and ET_{CO_2}

Breathing the CO_2/air mixture compared to air significantly increased respiratory rate 21±1 vs 13±1 breaths/min, ET_{CO_2} 7.0±0.2 vs 5.0±0.3 kPa, and oxygen saturation 98±0.2 vs 97±0.2%, respectively. There was no significant difference between T_2 (30 min posthypercapnia) and baseline.

Pulmonary Hemodynamics

Hypercapnia (T_1) was associated with a significant ($p<0.05$) increase in both MPAP and PVR compared

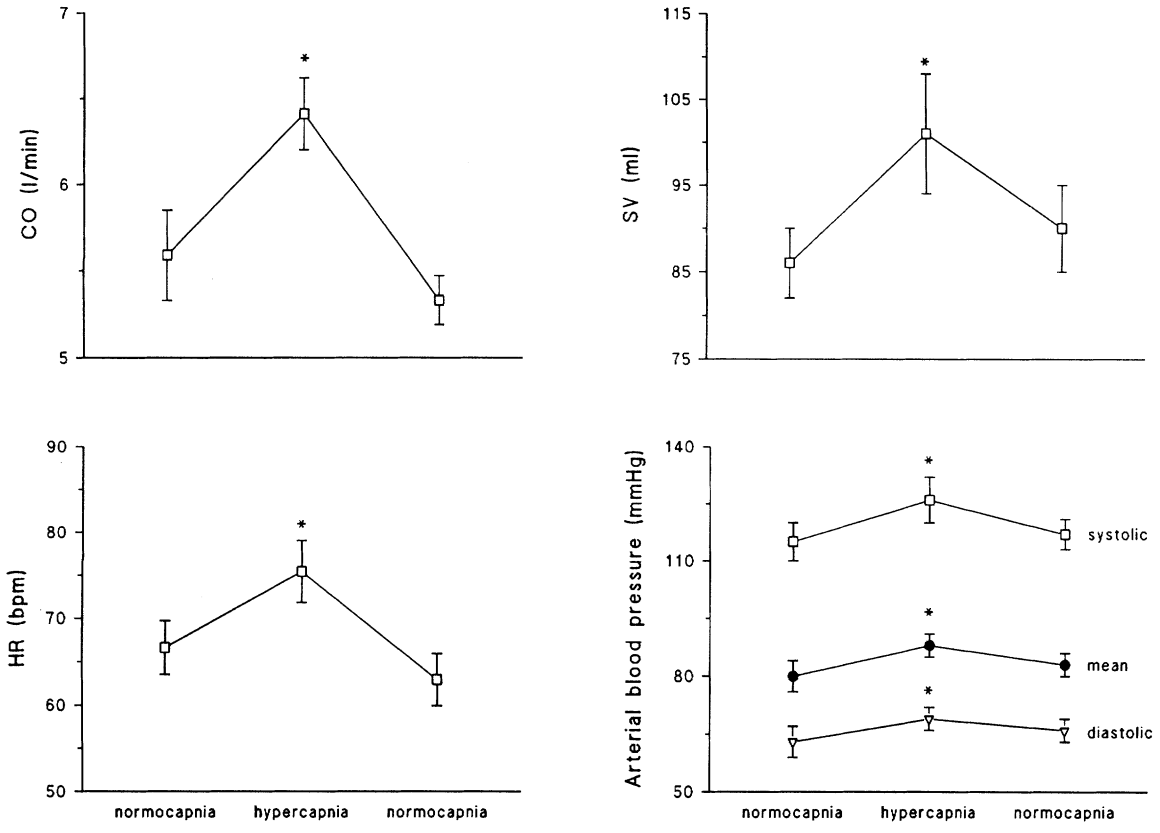

FIGURE 2. Effects of hypercapnia on systemic hemodynamic parameters. *Top left:* absolute CO measured during normoxemia (baseline), after 30 min hypercapnia, and 30 min after rebreathing air, respectively. *Bottom left:* absolute HR measured during normoxemia (baseline), after 30 min hypercapnia, and 30 min after rebreathing air, respectively. *Top right:* absolute SV measured during normoxemia (baseline), after 30 min hypercapnia, and 30 min after rebreathing air, respectively. *Bottom right:* absolute SBP (open squares), MAP (solid circles), and DBP (open triangles) measured during normoxemia (baseline), after 30 min hypercapnia, and 30 min rebreathing air, respectively. Asterisk=a significant ($p<0.05$) difference between baseline and hypercapnia.

with baseline (T_0) (Fig 1). There was no significant difference between T_2 (30 min posthypercapnia) and baseline.

Systemic Hemodynamics

Hypercapnia (T_1) was associated with a significant ($p<0.05$) increase in SBP, DBP, MAP, HR, and CO compared with baseline (T_0) (Fig 2). However, hypercapnia had no significant effect on systemic vascular resistance (SVR) compared with baseline: 1,102±38 vs 1,162±78 dyne·s·cm^{-5}. There was no significant difference between T_2 and T_0 for any of the systemic hemodynamic parameters.

Systolic Flow Parameters

Hypercapnia compared with baseline had no significant effect on Av_{peak}, Acc_{peak}, or Acc_{mean} (Table 1).

Table 1—*Hypercapnia and Its Effects on Systolic and Diastolic Parameters**

	T_0	T_1	T_2
Av_{peak}, ms^{-1}	1.20±0.08	1.26±0.10	1.15±0.05
Acc_{mean}, ms^{-2}	11.9±1.4	10.8±1.2	10.8±1.1
Acc_{peak}, ms^{-2}	26.8±4.0	24.8±3.6	28.1±3.6
Ev_{max}, ms^{-1}	77±5	75±6	71±5
Av_{max}, ms^{-1}	42±2	41±3	41±3
E/A ratio	1.86±0.17	1.90±0.21	1.81±0.19
EDT, ms	121±5	123±7	114±9
EDTc, ms	121±9	137±9	124±5
IVRT, ms	66 ± 5	65 ± 4	68 ± 3
IVRTc, ms	74±5	70±3	72±4

*There were no significant differences between T_0 (baseline), T_1 (ET_{CO_2}=7 kPa), and T_2 (after rebreathing air for 30 min) for each of the above variables.

Table 2—*Hypercapnia and Its Effects on the RAS*

	T_0	T_1	T_2
PRA, pmol/h/mL	1.21±0.31	1.00±0.21	0.57±0.15*
ANG II, pmol/L	15.8±2	19.0±4.7	13.2±1.4
ALDO, pmol/L	86.2±14.7	74.49±11.6	72.3±16.3

*A significant difference in PRA at T_2 (30 min after rebreathing air) compared with T_0 (baseline). There were no significant differences between T_1 ($ETCO_2$=7 kPa) and the other time points for any of the above variables.

Diastolic Flow Parameters

Similarly hypercapnia compared with baseline had no significant effect on Ev_{max}, Av_{max}, E/A ratio, EDT, EDTc, IVRT, or IVRTc (Table 1).

QT Dispersion

Hypercapnia compared with baseline had no significant effect on QT interval, although QTc was significantly increased after hypercapnia (Fig 1). Hypercapnia also significantly increased QT dispersion compared with baseline and this was also significantly elevated after 30 min rebreathing air compared with baseline.

Renin Angiotensin System (RAS) Activity

Hypercapnia had no significant effect on ANG II, PRA, or ALDO, although PRA was significantly lower at T_2 with baseline (Table 2).

Discussion

We have shown that acute hypercapnia causes true pulmonary vasoconstriction *in vivo* in normal volunteers as reflected by a significant increase in both MPAP and PVR. Although acute hypercapnia had no significant inotropic or lusitropic effects, it significantly increased QT dispersion, suggesting that hypercapnia may cause abnormalities in myocardial repolarization.

The effect of CO_2 on the pulmonary circulation in man remains controversial, although the evidence appears to suggest a vasoconstrictor effect.[8-13] We aimed to achieve $ETCO_2$ similar to that encountered in patients with exacerbations of COPD and also that found in permissive hypercapnia. Our mean $ETCO_2$ of 7 kPa equates with an arterial PCO_2 of approximately 7.5 kPa, and $ETCO_2$ is known to closely mirror the concentration of CO_2 in arterial blood.[29] Blood leaving the ventilated alveoli usually mixes with blood from both parenchymal lung tissue and with blood passing through nonventilated alveoli, creating a venous admixture. It is this venous admixture that accounts for the normal alveolar-arterial CO_2 tension difference. The early work of Fishman et al[9] looked at the effect of 3 to 5% CO_2 on the pulmonary vasculature in normal volunteers and in patients with COPD and concluded that breathing air rich in CO_2 had no effect on pulmonary vasoconstriction. This was in sharp contrast to work performed in animals and this apparent dichotomy was explained by Kilburn et al[8] who demonstrated pulmonary vasoconstriction in patients with COPD exposed to more severe hypercapnia. These findings have been corroborated in other studies in patients with elevated and normal MPAPs.[10,30] This study in normal humans provides further support for the evidence in patient studies that hypercapnia is a relatively weak pulmonary vasoconstrictor and that pulmonary vessels may be the exception to the rule that acidosis causes vasodilatation.[31] Thus, hypercapnia may function in humans as an intrinsic mechanism diverting blood from underventilated areas of the lung in an effort to maintain ventilation perfusion matching. In contrast to previous studies, we have used Doppler echocardiography to measure hemodynamic changes in the pulmonary circulation. These noninvasive techniques have been shown to be highly reproducible[22] and the close correlation between Doppler PAT and MPAP as measured by right heart catheter is well established.[24,32,33] We looked at two measures of pulmonary vasoconstriction: changes in MPAP and PVR. The use of total PVR does not account for any changes in the postcapillary vascular bed, as conventionally assessed by pulmonary capillary wedge pressure. In this respect we believe that it is unethical to insert Swan-Ganz catheters into normal volunteers for research purposes and the extra information this would give us is not essential. It has previously been shown that hypercapnia has no significant effects on pulmonary capillary wedge pressure either in patients with normal pulmonary artery pressures or those with elevated pressures occurring as a consequence of hypoxic lung disease and so effects on total PVR are reflective of changes in true PVR in precapillary arterioles during hypercapnia.[10] We believe, therefore, that the observed changes in total PVR are a true reflection of changes in pulmonary vascular tone.

The systemic effects of hypercapnia are complex and reflect a balance between the direct effects of CO_2 and the secondary effects of CO_2 mediated via the central and autonomic nervous systems. In this study, we have demonstrated significant increases in HR, SV, CO, SBP, MAP, and DBP and a nonsignificant reduction in SVR, changes that have previously been documented in patients with similar degrees of hypercapnia.[6,7]

Interestingly, although hypercapnia has been shown to be a direct myocardial depressant in the isolated

heart,[34,35] we have shown no significant effects of hypercapnia on either inotropic or lusitropic indexes of cardiac function measured using Doppler echocardiography. Mean and peak aortic acceleration as well as peak aortic velocity have been shown to be sensitive markers of left ventricular contractility.[16,36-38] Although Acc_{peak} and Av_{peak} decline with increasing HR[39] during pacing, the effects across our HR range are small and consistent with the nonsignificant changes observed. This suggests that the systolic contractility of the normal human myocardium is relatively resistant to the effects of acute hypercapnia. Similarly we have shown no effect on ventricular diastolic function, which is an important determinant of overall cardiovascular performance and a sensitive marker of cardiac dysfunction, as reflected by the lack of effect of hypercapnia on all of the measured indexes. This suggests that the secondary effects of hypercapnia on the central and autonomic nervous systems in the integrated physiologic system of humans are capable of antagonizing the direct myocardial depressant effects of hypercapnia.[40,41]

Although acute hypercapnia appears to have no significant effects on myocardial contractility, the observation that hypercapnia increases both QTc interval and QT dispersion suggests that it has significant effects on myocardial repolarization. The finding that hypercapnia increases QT dispersion is probably of more significance since this represents differences in regional myocardial repolarization and as such represents a putative substrate for arrhythmias. In contrast, QTc interval provides no information regarding regional repolarization abnormalities. Evidence suggests that QT dispersion is a sensitive index of the propensity for developing life-threatening arrhythmias and as such may lower the arrhythmogenic threshold in conditions in which hypercapnia exists. The mechanism whereby hypercapnia causes these abnormalities in myocardial repolarization may be related to its effects on autonomic function or elevated levels of catecholamines that have been previously demonstrated during acute hypercapnia.[42] QT dispersion is a useful, easily applicable noninvasive technique. We used a computer-linked digitizing tablet that has been shown by other investigators to be a reliable and accurate measure of QT dispersion.[26] Probably the most important aspect concerning methods is the protocol to define the end of the T wave. We have thus used the most commonly used protocol[20] and one that has been shown to correlate with arrhythmia risk and sudden death in patient studies.[43,44] We used routine ECGs to measure QT dispersion because we believed that this would have the most clinical relevance, and indeed no substantial evidence suggests that simultaneous ECG recording has any benefits.

We have also investigated the effect of acute hypercapnia on the RAS. In the absence of hypercapnia, RAS activation in hypoxemic patients is rare,[45] suggesting a possible role for hypercapnia possibly occurring as a consequence of renal vasoconstriction or as a result of a direct cellular effect. In this study, however, we were unable to demonstrate any significant effect of hypercapnia on PRA, ANG II, or ALDO. This may be related to the brevity of our stimulus, although similar periods of hypoxia suppressed ALDO levels.[46] It is also possible that hypoxia and hypercapnia may need to be present in synergistic fashion to produce clinically detectable RAS activation. The significant fall in PRA 30 min after cessation of hypercapnia compared with baseline is consistent with the known effects of resting in the supine position, in which values of PRA increase with upright body posture and fall with time when the supine position is assumed.[47,48]

To conclude, acute hypercapnia appears to have no effects on myocardial contractility or relaxation in the integrated physiologic system of humans, although repolarization abnormalities reflected by an increase in QT dispersion may provide an environment for arrhythmogenesis. We have also shown that hypercapnia causes true pulmonary vasoconstriction in humans. This agrees with findings in patient studies but also suggests that *in vivo*, hypercapnia has a role to play in modulating pulmonary blood flow in healthy humans.

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