SEX-RELATED DIFFERENCES IN PLATELET MORPHOLOGY IN WHOLE BLOOD (WB) AND PLATELET-RICH PLASMA (PRP)

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(Received 10.6.1982; Accepted in revised form 22.3.1983 by Editor J. Hirsh)

ABSTRACT The proportion of smooth, disc-shaped platelets (D) in freshly drawn, glutaraldehyde fixed whole blood (WB) and citrated platelet-rich plasma prepared at 37°C is compared for male (N = 55) and female (N = 31) donors. Female donors have significantly more D than male donors and the variability in D measured on repeated occasions over a period of 3-69 months is less for female donors. WB and PRP gave similar results. The sex-related differences in D were not related to hematocrit or to concomitant use of oral contraceptives. There were no significant sex-related differences in platelet mean volume or in platelet plasma membrane surface area as determined by the osmotic spherocyte method. However, the volume of D is smaller for male donors. It is concluded that the sex-related differences in platelet morphology do not represent intrinsic differences in platelet size or measurable total plasma membrane but represent a selective shape change activation of the larger D in the circulation of male donors. The significance of these observations for the sex-related differences in risk of cardiovascular disease and efficacy of anti-thrombotic therapy awaits appropriate prospective epidemiological studies.

INTRODUCTION

Platelets play an important role in the pathogenesis of atherosclerosis [1-2]. Before menopause, women have a lower incidence of the clinical complications of atherosclerosis than men of the same age [3]. Moreover, results of various clinical trials have now raised the possibility that the beneficial effects of anti-platelet drugs, such as aspirin and sulfinpyrazone, may be much less apparent in females than males [4-5]. The extent to which these observations reflect sex-related difference in platelet function is unsettled.

Key Words: Platelet morphology, size, surface area, sex differences.
Several laboratories have reported sex-related differences in ADP-induced platelet aggregation in citrated platelet-rich plasma (PRP) [6-7]. One group has suggested that these differences merely reflect differences in the citrate concentration in the isolated PRP due to differences in blood hematocrit [8]; however, this has not been confirmed by others [9]. Studies of inhibition by aspirin of platelet cyclo-oxygenase and the absorption of aspirin have failed to explain the sex-related difference in the antithrombotic effect of aspirin [10]. Lastly, there are no sex-related differences in the platelet utilization of arachidonic acid [11].

Whether or not there are sex-related differences in platelet structure and morphology has received little attention. Here we compare morphology, size and membrane surface area of platelets in whole blood (WB) and PRP for male and female donors.

**MATERIALS AND METHODS**

Healthy donors were 55 males and 31 females typically between the ages of 18 and 30 (6 males and 5 females greater than 30 yrs.) seen in our laboratory over the last 5 1/2 years. Donors had not taken aspirin in one week prior to donating blood. Blood was drawn from the antecubital vein using a 19-G butterfly needle and a plastic syringe. The first 1-2 cc blood was discarded and the blood for investigation (typically 40-60 cc) was drawn into a fresh plastic syringe. For a detailed discussion of the precautions necessary to preserve platelet morphology during venipuncture and the constancy of platelet morphology for final % glutaraldehyde in whole blood or PRP varying from 0.5-1%, see reference [12]. One cc of the blood was immediately added to 4 ml 0.8% glutaraldehyde (v/v) in Tyrodes, pH 7.4, 37°C (within < 30 seconds of drawing blood), a sample taken for hematocrit determination, the remaining blood was added to 3.8% citrate (1 vol to 9 vol blood) and PRP prepared as described previously [13]. PRP was allowed to stand at 37°C under 5-6% CO2 for 30 minutes after centrifugation before a sample was fixed for determination of platelet size and morphology (0.1 cc PRP into 0.4 cc 0.8% glutaraldehyde). Samples for determining platelet morphology in WB were prepared by allowing the glutaraldehyde-fixed WB to stand at 1 g until sufficient supernatant formed to be able to draw 1 drop with a pipette and transfer to a glass slide (typically 30 minutes). Samples of WB and PRP for platelet morphology were prepared on the same day that blood was drawn, were typically measured on the same day, but could be analyzed up to 5 days later with no measurable changes in platelet morphology. Platelet morphology distributions for donors seen 3-5 years ago were taken from cinema photomicrographs (no difference in platelet morphology distribution from fresh samples and from cinema photomicrographs).

Osmotic spherocytes were prepared by slowly adding 4 volumes distilled water, 37°C to 1 volume PRP as described previously [14] and spherocyte size was measured between 12-20 minutes post-water addition.

Platelet morphology was classified from the appearance of platelets under phase contrast microscopy (40 x objective; Zeiss Universal Microscope) [12, 15-16]: 1) edge-on discocytes (D) appear as smooth ellipsoids (axial ratio (thickness/diameter) less than 0.5), whereas face-on they appear circular, 2) spher-echinocytes (SE) appear circular (axial ratio greater than 0.9) with a white center in all orientations, and 3) disco-echinocytes (DE) are all those platelets which do not satisfy the criteria for D and DE. For examples
of photomicrographs of D, DE and SE see reference [12]. This classification
yields highly reproducible results (distribution of platelet morphology to
within < 5% D, < 5% DE, < 1% SE between several investigators in the same or
different laboratories counting the same sample and < 2% D, < 2% DE, < 1% SE
for a single, experienced investigator).

Platelet geometry was determined by the cinematographic method described
previously [16]. Platelet mean volume ($V_T$) was determined from the relation

$$V_T = f_D V_D + f_{DE} V_{DE} + f_{SE} V_{SE}$$

where, respectively, $f_D$, $f_{DE}$, $f_{SE}$, $V_D$, $V_{DE}$, $V_{SE}$ are the fractions and mean
volumes of D, DE, SE. Platelet volumes of DE and SE were corrected for the
contribution of pseudopods as described previously [17]. Correcting for the
volume contribution of pseudopods increases $V_T$ by < 2%.

RESULTS

Platelet Morphology in WB and PRP

Platelet morphology (%D) was measured for 31 female donors examined on a
total of 71 occasions and for 55 male donors examined on a total of 123 oc-
cassions. Each donor was examined on an average of 2 occasions (range 1-11)
over a period of 5 1/2 years. Platelet morphology was evaluated in both WB
and PRP on 48 occasions and in the remaining cases either in PRP (N=113) or in
WB (N=33) alone. There was no significant difference in %D between WB and
PRP (mean %D 59.4% versus 59.5%, respectively; N=48; P>>0.8 for a paired t
-test, two tailed).

Figure 1 compares platelet morphology (%D) for male (N=55) and female
(N=31) donors. Each point represents one donor. In the case of donors which
had platelet morphology evaluated on more than one occasion the representat-
ive point was randomly selected from all the measurements made for that donor
(WB and PRP). The proportion of discocytes (%D) observed for female donors is
greater than for male donors (69 ± 10% (mean ± SD) versus 60 ± 11% for male
donors). This difference in %D is statistically significant (P<0.001 for a
two-tailed t test). Identical conclusions were reached when 1) only data
from PRP or WB was analyzed (see legend for Figure 1), 2) all measurements
were analyzed (data not shown) and 3) for each donor the mean %D was analyzed
(data not shown).

In view of the above considerations we conclude that blood from female
donors contains a significantly higher %D than male donors and that this con-
cclusion is independent of the method chosen to analyze the data.

Independence of Platelet Morphology on Hematocrit

Table 1 compares the correlation between platelet morphology (%D) and
hematocrit (Hct) for donors examined on a minimum of 4 occasions. In all
cases no significant correlation between %D and Hct can be demonstrated. Thus
changes in Hct which presumably arise through normal physiological mech-
isms do not influence platelet morphology.

Figure 2 compares %D versus Hct for male (N=23) and female (N=12) donors.
### TABLE 1

Correlation Between Changes in %D and Hematocrit for Male and Female Donors

<table>
<thead>
<tr>
<th>Donor</th>
<th>Number of Occasions</th>
<th>Range of Hematocrit Change</th>
<th>Range of % Change</th>
<th>Correlation Coefficient</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor 1</td>
<td>4</td>
<td>41-44</td>
<td>61-68</td>
<td>0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Donor 2</td>
<td>4</td>
<td>43-46</td>
<td>59-64</td>
<td>0.91</td>
<td>NS</td>
</tr>
<tr>
<td>Donor 3</td>
<td>4</td>
<td>42-45</td>
<td>62-72</td>
<td>-0.24</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor a</td>
<td>9</td>
<td>40-48</td>
<td>50-68</td>
<td>0.38</td>
<td>NS</td>
</tr>
<tr>
<td>Donor b</td>
<td>9</td>
<td>45-48</td>
<td>40-65</td>
<td>-0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Donor c</td>
<td>7</td>
<td>42-48</td>
<td>47-75</td>
<td>-0.39</td>
<td>NS</td>
</tr>
<tr>
<td>Donor d</td>
<td>5</td>
<td>46-48</td>
<td>46-61</td>
<td>-0.27</td>
<td>NS</td>
</tr>
</tbody>
</table>

1. Range shows the lowest and highest value obtained.
2. Donor 1 was taking oral contraceptives, whereas donors 2 and 3 were not.

As for Figure 1, each point in this Figure represents a single donor and for those donors examined on more than one occasion the representative point (%D and corresponding Hct) was chosen randomly. For female donors there was no significant correlation between %D and Hct over the range 39-47% (correlation coefficient (CC) = -0.20, P>0.05). For male donors no significant correlation exists between %D and Hct over the range 43-50% (CC = -0.14, P>0.05). On disregarding the sex of the donor, a statistically significant correlation was found between %D and Hct over the range 39-50% (CC = -0.45, P<0.01). Since 1) the ranges of Hct observed for male and female overlap and are only slightly smaller than the range of Hct observed for pooled male and female donors and 2) no correlation exists between %D and Hct for male or female donors, it follows that the significant correlation between %D and Hct observed for pooled male and female donors is spurious and merely reflects the fact that female donors tend to have lower Hct and higher %D than males. This conclusion is supported by the observation that if the range of hematocrit was restricted to only that which contained both male and female data points, i.e. 43-47% (see Figure 2), then a statistically significant correlation between %D and Hct can no longer be demonstrated (CC = -0.24, P>0.05).

In view of the above observations it was concluded that no significant correlation exists between platelet morphology and hematocrit whether the latter changes arise from intra-donor or inter-donor variation. Thus the differences in platelet morphology between male and female donors shown
in Figure 1 cannot be accounted for by the influence of hematocrit.

Long-Term Variability of Platelet Morphology in PRP

Table 2 compares platelet morphology for a number of male and female donors examined on a minimum of 3 occasions over a period not less than 3 months. The average difference between the minimum and maximum %D divided by the mean %D, ΔD, is smaller for female donors (0.15 versus 0.35). Using a non-parametric method to test the significance of this difference, i.e. Wilcoxon rank sum test, it is found that the difference between ΔD for male and female donors is statistically significant (0.001 < P < 0.01). Thus not only do female donors have platelet populations with a higher proportion of D, there is also a tendency for the platelet morphology to be less variable.

![Graph](image)

**FIG. 1**

Comparison of the proportion of discocytes in blood for male and female donors. Each point represents one donor and was determined as described in text. Boxes enclose ± 2 SD and mean is indicated by longer horizontal line. In PRP, %D was 61.5 ± 70% for male donors (N=51) and 71 ± 10.5% for female donors (N=28) (P<0.001 for a two-tailed t-test). In WB, %D was 58 ± 11% for male donors (N=24) and 65.5 ± 8.5% for female donors (N=15) (P<0.05 for a two-tailed t-test).
### TABLE 2

Long-Term Variability in %D For Male and Female Donors

<table>
<thead>
<tr>
<th>Donor</th>
<th>Average %D</th>
<th>Time Donor Followed (months)</th>
<th>Number of Occasions</th>
<th>$\Delta D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor a</td>
<td>75</td>
<td>5</td>
<td>4</td>
<td>0.17</td>
</tr>
<tr>
<td>Donor b</td>
<td>69</td>
<td>13</td>
<td>4</td>
<td>0.23</td>
</tr>
<tr>
<td>Donor c</td>
<td>82</td>
<td>15</td>
<td>6</td>
<td>0.14</td>
</tr>
<tr>
<td>Donor d</td>
<td>75</td>
<td>9</td>
<td>3</td>
<td>0.10</td>
</tr>
<tr>
<td>Donor e</td>
<td>69</td>
<td>69</td>
<td>8</td>
<td>0.15</td>
</tr>
<tr>
<td>Donor f</td>
<td>64</td>
<td>5</td>
<td>3</td>
<td>0.09</td>
</tr>
<tr>
<td>Donor g</td>
<td>74</td>
<td>5</td>
<td>3</td>
<td>0.18</td>
</tr>
<tr>
<td>Donor h</td>
<td>76</td>
<td>16</td>
<td>4</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Mean = $0.15 \pm 0.04^4$

<table>
<thead>
<tr>
<th>Male 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor 1</td>
</tr>
<tr>
<td>Donor 2</td>
</tr>
<tr>
<td>Donor 3</td>
</tr>
<tr>
<td>Donor 4</td>
</tr>
<tr>
<td>Donor 5</td>
</tr>
<tr>
<td>Donor 6</td>
</tr>
<tr>
<td>Donor 7</td>
</tr>
<tr>
<td>Donor 8</td>
</tr>
<tr>
<td>Donor 9</td>
</tr>
<tr>
<td>Donor 10</td>
</tr>
<tr>
<td>Donor 11</td>
</tr>
</tbody>
</table>

Mean = $0.36 \pm 0.15^4$

1) $\Delta D = (\text{Maximum } %D \text{ observed minus minimum } %D \text{ observed})/\text{average } %D$.
2) For this group of female donors, %D = 73.0 ± 5.5% and this is not significantly different from the larger population in Figure 1.
3) For this group of male donors, %D = 63.9 ± 9.3% and this is not significantly different from the larger population in Figure 1.
4) Values are mean ± 1 S.D.
Proportion of discocytes (%D) for male and female donors as a function of hematocrit. For females the correlation coefficient in WB and PRP were, respectively, 0.08 (N=9) and -0.07 (N=10) and for male donors' -0.15 (N=15) and -0.31 (N=21). These correlation coefficients were not significantly different from zero (P>0.05).

Influence of Oral Contraceptives on %D

%D for female donors taking oral contraceptives was 72.4 ± 6.5% (N=5) versus 69.9 ± 6.2% (N=16) for those not taking oral contraceptives (the remaining 9 female donors could not be reached to determine whether or not they were taking oral contraceptives). These differences are not statistically significant (P>0.4 for a two-tailed t-test).

Platelet Size in PRP

Table 3 compares mean platelet volume (VT) and platelet volume as a function of morphology (VD, VDE) for platelets in PRP from female and male donors. There is no significant sex-related differences in VT and VDE; however, VD is smaller for male donors.

Platelet Osmotic Spherocyte Size

Table 4 shows that there is no significant difference in surface area and volume for osmotic spherocytes prepared from male and female platelets.
# TABLE 3

Comparison of Platelet Size in PRP for Male and Female Donors

<table>
<thead>
<tr>
<th></th>
<th>%D</th>
<th>$V_D$ (µm$^3$)</th>
<th>$V_{DE}$ (µm$^3$)</th>
<th>$V_{DE/V_D}$</th>
<th>$V_T$ (µm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>♀</td>
<td>69.9 ± 5.7$^1$</td>
<td>5.7 ± 0.7</td>
<td>7.2 ± 1.2</td>
<td>1.3 ± 0.2</td>
<td>6.1 ± 0.7</td>
</tr>
<tr>
<td>(N = 16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>♂</td>
<td>63.8 ± 9.0</td>
<td>5.1 ± 0.8</td>
<td>7.2 ± 1.3</td>
<td>1.4 ± 0.1</td>
<td>5.9 ± 0.9</td>
</tr>
<tr>
<td>(N = 19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of Significance</td>
<td>P &lt; 0.025</td>
<td>N.S.</td>
<td>P &lt; 0.01</td>
<td>N.S.</td>
<td></td>
</tr>
</tbody>
</table>

$^1$ Sub-populations of male and female donors do not significantly differ from the whole population in Figure 1. Values reported are mean ± 1 S.D.

# TABLE 4

Comparison of Osmotic Spherocyte Geometry of Platelets From Male and Female Donors

<table>
<thead>
<tr>
<th></th>
<th>%D</th>
<th>Surface Area (µm$^2$)</th>
<th>Volume (µm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>♀</td>
<td>68.6 ± 6.1$^1$</td>
<td>35.4 ± 3.8</td>
<td>19.9 ± 3.7</td>
</tr>
<tr>
<td>(N = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>♂</td>
<td>62.7 ± 8.4$^1$</td>
<td>35.1 ± 4.8</td>
<td>19.5 ± 5.0</td>
</tr>
<tr>
<td>(N = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of Significance</td>
<td>P &lt; 0.05</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

$^1$ Sub-populations of male and female donors do not significantly differ from the whole population in Figure 1. Values reported are mean ± 1 S.D.
DISCUSSION

We have compared platelet morphology between male and female donors. On average, platelets from female donors have a higher proportion of discocytes than those from male donors of the same age. These differences in platelet morphology are not correlated with hematocrit. It is widely held that platelet morphology in freshly drawn blood that is immediately fixed with buffered glutaraldehyde closely resembles that of platelets in circulation [12, 18-20]; though this may not be true in certain clinical conditions [18]. Thus the above observations suggest that there is a higher proportion of circulating platelets in female donors that are discocytes than for male donors. Although there are no differences between the mean volume ($V_T$) or male and female platelets, male discocytes are smaller.

The above sex-related differences in platelet morphology could in principle reflect differences at the level of platelet production and/or post-production. Large platelets are metabolically and functionally more active than smaller ones [22], and moreover become smaller, as they age in circulation, by progressive membrane loss [23]. Thus it is possible to decide at what level the difference in platelet morphology occurs by measuring platelet plasma membrane.

There are no sex-related differences in the volume ($V_S$) or surface area (SA) of osmotic spherocytes. It has been suggested that osmotic spherocytes are formed by an evagination of the open canalicular system (OCS) of platelets [14] and that SA provides a measure of the total membrane surface area demarcated by the megakaryocyte during platelet production [24]. This observation would suggest that at the level of platelet production by the megakaryocyte there are no sex-related differences. This suggests that the sex-related differences in platelet morphology reflect events which follow demarcation of platelet membrane by the megakaryocyte during platelet production. It is unlikely that these differences reflect a selective activation of larger platelets during venipuncture since in acquired platelet disorders in which shape change activation occurs during venipuncture there is a wide discrepancy between SD in WB and PRP [21] in contrast to the identical %D seen in WB and PRP reported here for female and male donors.

The initial shape of platelets produced by a fragmentation process in the megakaryocyte is presumably non-discoid and hence D arise by a reorganization of the membrane following platelet production [12]. Hence it is possible that there are differences in the relative ability of male and female platelets to become D from precursor fragments. In addition, it is possible that in the course of on-going reversible activation in the circulation, the expected reversion of early DE to D [12] may be considerably reduced for males than for females. However, we have observed no differences in the ability of platelet shape to revert to D following shape change induced by ADP in vitro for female and male donors (%D at 30 minutes post 1 μM ADP/initial %D equal 0.74 ± 0.18 and 0.64 ± 0.14, respectively, for female ($N = 5$) and male ($N = 5$) donors; not significantly different, $P > 0.3$ for a two-tailed t-test).

In view of the above observations we suggest that the sex-related differences in platelet morphology reflect an enhanced "shape-change associated activation" of the larger D in the circulation of male donors. As a corollary, this activation must be sufficiently mild as to not produce the more advanced morphological changes seen in PRP treated with high activator concentrations (see 12) or seen in WB in certain clinical conditions [12], nor to alter platelet production.
Although platelet activation and shape change normally accompany most in vitro measured platelet functions, the relation between final platelet shape and measured platelet functions is complicated by the time-dependent changes in platelet shape, accompanying membrane biochemistry, and history of intracellular events (12); for example, platelets shape-changed by activators show normal subsequent uptake of serotonin, if and only if, no major release reaction has been induced, while von Willebrand Factor VIII binding to platelets is suppressed by prior ADP-induced shape change (see Chaps. XII-D and A respectively (12)). In this regard, the recent report showing decreased responsiveness of male platelets to release of serotonin induced by immune complexes in isolated washed platelets, as compared to female platelets (25) may be associated with the increased activation of platelets identified from studies of morphology herein reported, with the precise mechanism(s) remaining to be determined. It is also possible that "shape-change associated activation" reflects intravascular events with no demonstrable in vitro-measured platelet function alterations.

It is possible that the sex-related differences in platelet morphology we have observed are, at least, partially related to hormonal influences. The observation that platelet morphology is less variable in female donors suggests that cyclic variations in female sex hormones of the magnitude seen in healthy females of reproductive age have little influence on platelet morphology. However, these observations do not exclude the possibility that the baseline level of female hormones is sufficient to maintain a high %D. Of interest in this respect is the observation that estrogens increase PGI2 levels in the female rat [26]. On the other hand, in vitro studies on the influence of sex hormones on platelet aggregation have suggested that preincubation of platelets with androgenic steroids enhances platelet aggregation to a greater extent than does estradiol or progesterone [6]. It is also possible that platelet morphology in circulation is influenced by interaction with various clotting factors, fibrinogen, plasminogen and fibrinolytic inhibitors; the levels of which are known to be sex hormone-dependent [27].

Hattori et al [18] have examined platelet morphology in WB of Japanese donors. Their results suggest a higher proportion of smooth, disc-shaped platelets in WB than we observe and although there was a slight tendency for female donors to have higher %D this trend was not statistically significant. It is unclear whether these differences from our results reflect the fact that they use different criteria for classifying platelet morphology or are possibly etiologically related to the observation that Japanese are at much lower risk for cardiovascular disease than North Americans [3].

The observations in this communication strongly suggest that measurements of subtle differences in platelet morphology can be utilized to monitor differences in circulating platelet populations. Presently, there appears to be no other technique available capable of providing equivalent information. In particular, measurements restricted to %D will be incapable of revealing sex-related differences. These observations support an earlier suggestion that for many platelet problems platelet mean size is of lesser importance than considerations of the interplay between morphology and size [17].

The age group we have examined is younger than the age group which are at greatest risk for the complications of atherosclerosis. Determining the etiological significance of differences in %D requires a large scale prospective epidemiological study. Certainly measurements of platelet morphology are well suited to this type of investigation; however, to date there is no study which
has incorporated this measurement. In our experience the method we have
developed for measuring platelet morphology is easily learned, highly reproduc-
tible, requires only a small blood sample (~1ml) and takes little time (~3
minutes).

The observations presented here raise the possibility that sex-related
differences in a) the incidence of atherosclerosis complications and b) the
efficacy of anti-platelet drugs may be related to those factors which determine
(or are reflected by) the morphology of platelets in circulation. In other
words the differences may not be related to intrinsic platelet properties as
much as to differences in the intravascular milieu. Little is known about the
nature of factors which determine circulating platelet morphology. It is hoped
that this communication will spark interest into the mechanisms which regulate
circulating platelet morphology and the possible relevance of this to diseases
in which platelets are thought to play a role.

ACKNOWLEDGEMENTS

Dr. Milton is supported by a medical scientist fellowship provided by the
Canadian Heart Foundation. The support of research by grants from the Medical
Research Council of Canada and the Quebec Heart Foundation are gratefully ack-
nowledged. The assistance of Drs. H. Ghezzo (Meakins Christie Laboratory) and
M. Mackey (Dept. Physiology, McGill University) is acknowledged for data mani-
pulation and statistical analysis.

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